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THE ACUTE MORTALITY RESPONSE OF MONKEYS (MACACA MULATTA) TO MIXED GAMMA-NEUTRON RADIATIONS AND 250 KVP X RAYS

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The mammalian responses to mixed gamma-neutron radiations are under intensive study at the Armed Forces Radiobiology Research Institute (AFRRI). The monkey (Macaca mulatta) has been the experimental animal of choice in several studies, particularly those concerned with incapacitation and behavioral decrements following lethal and superlethal exposures. The present study was undertaken as one essential phase of characterizing the lethal and clinical responses of the Macaca mulatta to mixed gamma-neutron radiations. Further, it represents an orderly progression, using various laboratory mammals, in evaluating median lethality from such radiations compared to a common reference source.

The monkeys were "wild-caught". They ranged in age from 2 to 5 years, weighed from 3.1 to 5.5 kilograms, and were equally distributed as to sex. Each animal had been conditioned for a minimum of 10 weeks and each had been tuberculin tested a minimum of five times. Beginning 2 weeks before irradiation and continuing throughout the 60-day postirradiation period, no therapeutic agents were administered. The basic diet was pelleted Purina monkey chow. The diet and frequency of feeding (3 times each day) were the same before and after irradiation. Food was available up to 1 hour before exposure.

The number of animals used in each part of the study is shown in Table I. The x irradiations were accomplished with the radial beam of a 250 kVp x-ray generator. The AFRRI-TRIGA reactor was the source of the mixed gamma-neutron radiations. For simplicity of presentation, the mixed gamma-neutron radiations will be referred to as reactor radiations in the remainder of this report. Sixty animals were exposed to x rays and 80 to reactor radiations. Including controls, 80 animals were designated

for x ray and 110 for the reactor radiations. A total of 190 animals was used in this study.

Table I. Total Animals

Radiation field	Irradiated	Controls	Totals
x-ray	60	20	80
mixed gamma-neutron (reactor)	80	30	110

Six exposure points were used in x ray and 8 in the reactor radiations (Table II). Each exposure point consisted of 10 animals, simultaneously exposed. The exposure range in the x-ray facility was 380 to 665 rads and in the reactor radiations, 304 to 567 rads. The x-ray measured exposure in roentgens was converted to rads using the mean conversion factor ($\bar{f}$) of 0.95 obtained from the International Commission on Radiological Units and Measurements (ICRU) Report 10b (National Bureau of Standards Handbook 85) for an x-ray generator with a tube potential of 250 kV and a HVL of 1.9 mm Cu.

Table II. Radiation Exposures

Radiation field	Number of points	Exposure range
x-ray	6*	380-665 rads
reactor	8*	304-567 rads

* 10 animals at each exposure point

Figure 1 illustrates the 10 positions on the circular exposure array in the x-ray facility. The room is 6 meters square. The source to midline exposure volume

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distance was 105 centimeters. The x-ray generator was operated at 250 kilovolts and 30 milliamperes producing, with filtration, a HVL of 1.9 mm Cu (effective energy of 106 kilovolts). The dose rate in a Plexiglas phantom at the center of the exposure volume (pyramid-shaped restraint box) was 20 rads per minute.

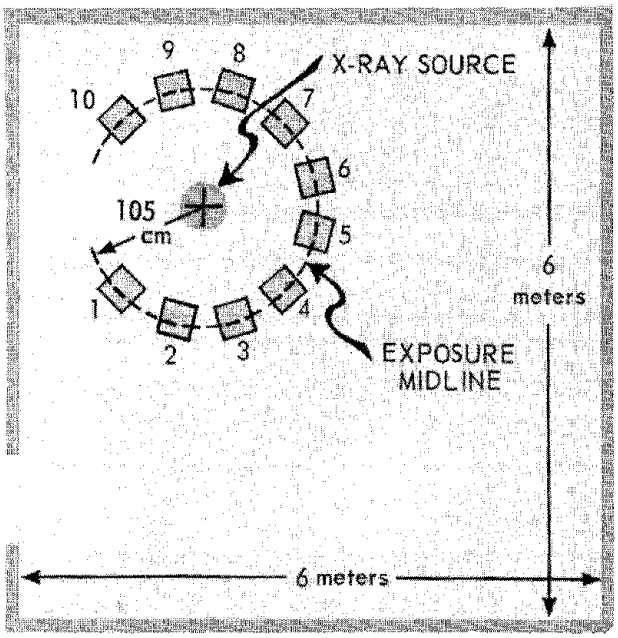

Figure 1. Plan view of x-ray facility

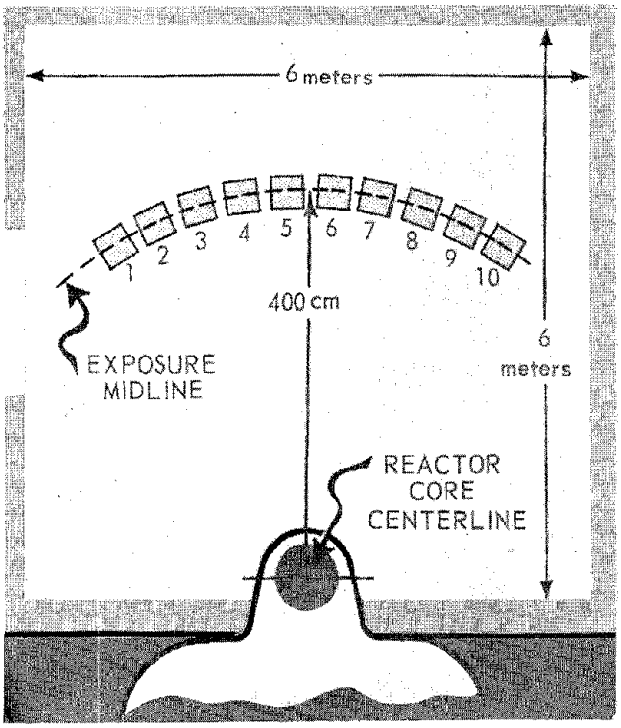

Figure 2. Plan view of reactor exposure room

Figure 2 shows the 10 positions on an isodose exposure arc in the reactor exposure room. This room is also 6 meters square. The distance from the reactor core centerline to the center of the exposure volumes was 400 centimeters. The dose rate in a Plexiglas phantom at the center of the exposure volumes was about 16 rads per minute. Sixty percent of the dose was gamma and 40 percent was neutron. The effective energy of the

gamma was between 1 and 2 MeV. About 75 percent of the neutron dose was attributed to fast neutrons (greater than 10 keV). The remaining 25 percent was from neutrons of lower energies.

Figure 3 shows the animals in the circular exposure array in the x-ray facility. Seven of the 10 animals are visible. The Plexiglas restraint box was clamped to a turntable, the latter being mounted on a wood stand. Each turntable was individually

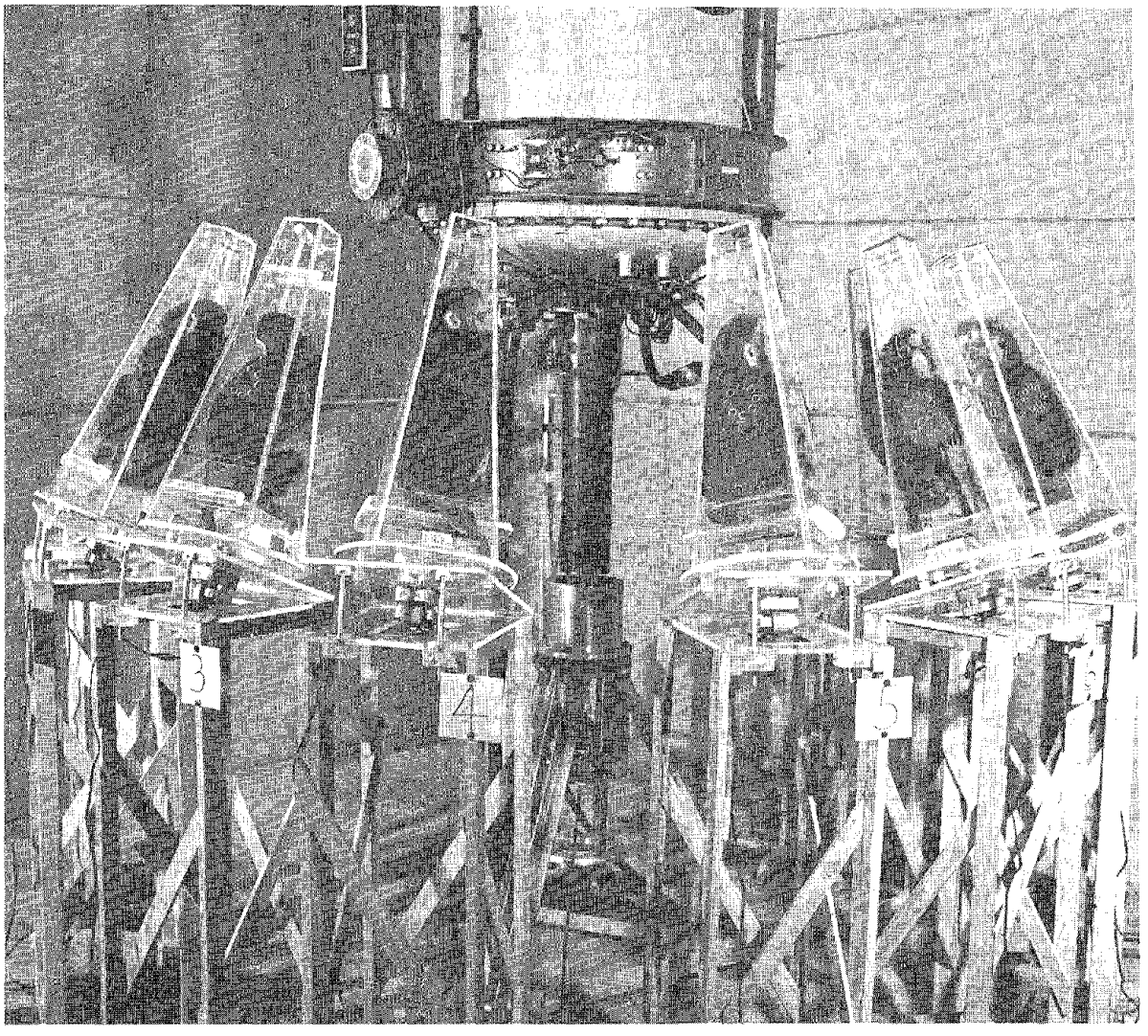

Figure 3. Animal array in x-ray exposure facility

driven by a small electric motor at 1 revolution per minute. Each restraint box was tilted 22-1/2 degrees to confine the dose falloff of the isodose exposure field to not more than 5 percent. A Victoreen Rate Meter was used to monitor each exposure. Dosimetry was accomplished in a Plexiglas phantom in these exposure positions.

Ten animals are shown in the reactor radiations exposure room (Figure 4). The mechanical arrangements for animal restraint and rotation were the same as shown in the x-ray facility, except for the tilt. In this exposure room, tilt was not required due to the more uniform isodose field. Extensive dosimetry was used in each exposure.

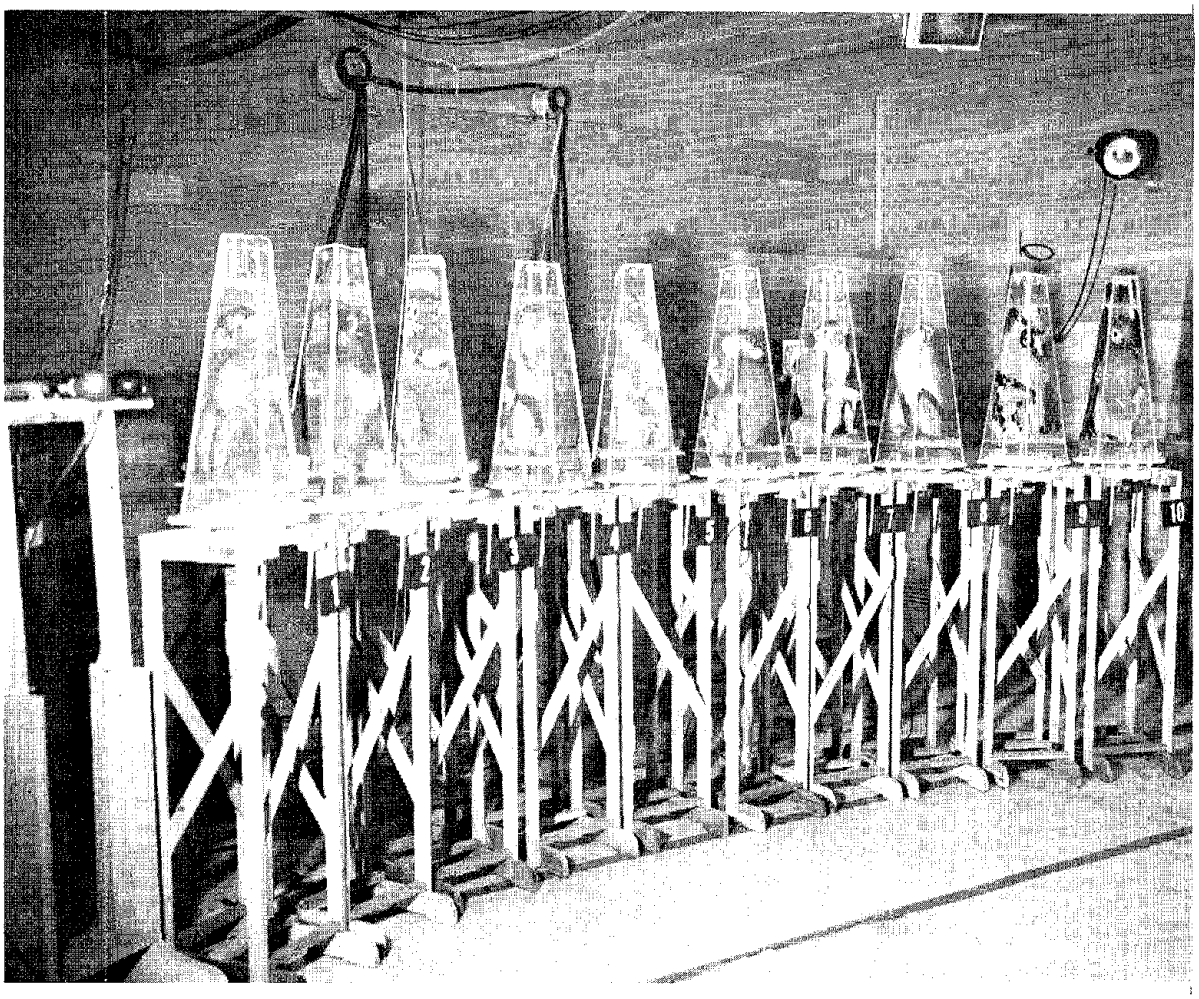

Figure 4. Animal array in reactor exposure room

The paired ionization chambers as seen on the far left were used for radiation monitoring. Sulfur tablets were placed on the front of each stand and shielded glass rods on the first, fifth and tenth stands as additional monitors. Dosimetry was also accomplished in these exposure positions using the monkey phantom.

All exposures in this study are reported as midline phantom, referenced to the center of a Plexiglas phantom, cylindrical in shape, that was placed in the center of the pyramid-shaped restraint box (exposure volume). Figure 5 illustrates the dose profiles for the two radiation fields in the phantom expressed as percent of midline phantom. Distance from surface to midline of the phantom at the chest level is shown in centimeters. Because there is a centerline of symmetry in the phantom, the data are presented for one side. Both exposures were "Class A, uniform," as defined in ICRU Report 10e (National Bureau of Standards Handbook 88).

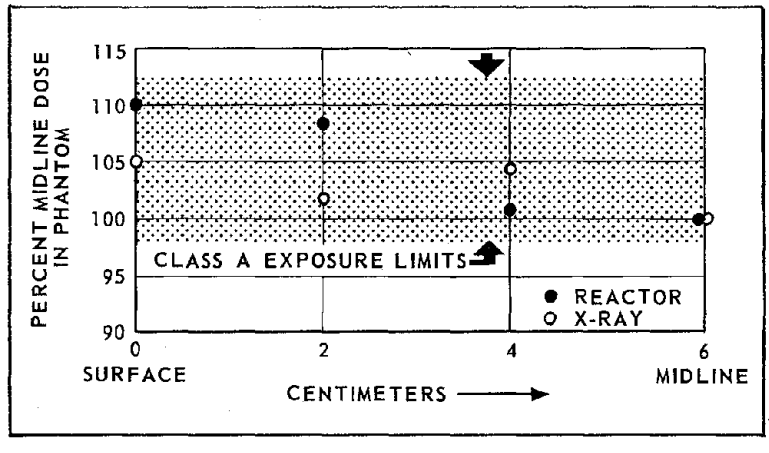

Figure 5. Dose profiles in monkey phantom (chest level)

Table III presents the raw data 60-day percent mortalities. In the x-ray exposures, 380 rads was the 10 percent mortality point and 665 rads was the 90 percent mortality point. Four additional mortality points were obtained in the interval between

the 10 and 90 percent points. In the reactor radiations exposures, 304 rads was the 10 percent point and 515 rads was the 90 percent point. Five additional points were obtained in the 304 to 515 rads lethal exposure interval. The 567 rads reactor radiations exposure caused 100 percent mortality. There was no mortality in the 50 controls.

Table III. Mortalities

Radiation field	10 percent point	Exposure points between	90 percent point
x-ray	380 rads	4	665 rads
reactor	304 rads	5	515 rads

100 percent mortality in the 567 rads reactor radiations exposure

No control mortality

The data were analyzed with an IBM 1620 Computer using a probit program developed by the United States Department of Agriculture. Figure 6 illustrates the computed results, with percent mortality shown on the ordinate and dose on the

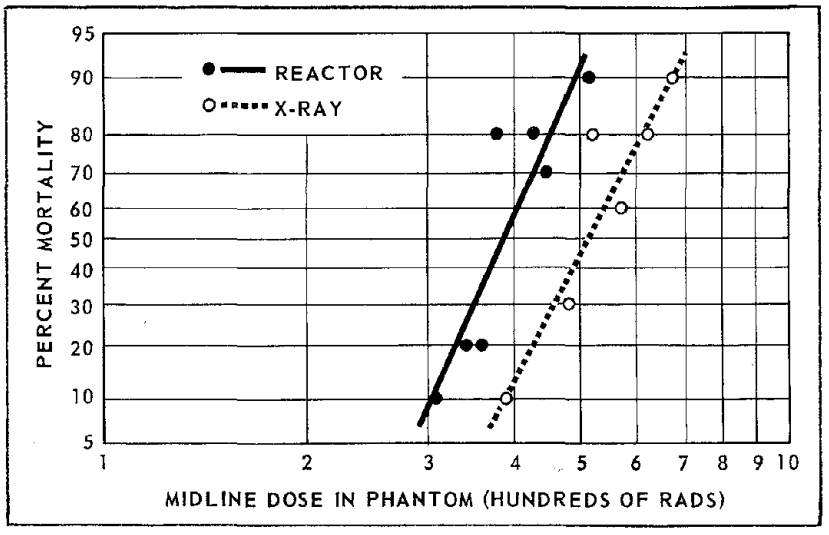

Figure 6. Dose-mortality regression lines

abscissa. The dose-response regression line for reactor radiations and the raw data points are shown as well as the x-ray regression line and the raw data points.

Table IV shows the 60-day median lethal doses for x ray and reactor radiations as obtained from the data analyses. The computed 50 percent lethal dose for x-ray exposures was 503 rads and for reactor radiations, 381 rads. The corresponding 95 percent confidence limits are also shown. The Relative Biological Effectiveness (RBE) of the reactor radiations to produce acute mortality, under the conditions of this study, is calculated to be 1.3 (95 percent confidence limits of 1.1 - 1.5).

Table IV. Median Lethality Data

Radiation field	60-day median lethal dose	95 percent confidence limits
x-ray	503 rads	448-546 rads
reactor*	381 rads	365-408 rads

* RBE of 1.3

Table V shows the comparability of mortality distributions in the two lethal ranges (excluding the superlethal 567-rad dose group). Of the 35 mortalities from x-ray exposures, 31 occurred in the 10 to 19-day interval. Thirty-six of the 37 mortalities from reactor radiations exposures occurred in that same interval. No deaths occurred after 30 days.

Vomiting occurred in 135 of the 140 irradiated animals in the 72 hours immediately following irradiation. One hundred and thirty-two had vomited one or more times by the end of the 3rd hour. Other early postirradiation symptoms were

polydipsia, anorexia, and diarrhea. Integumentary petechiations were observed in most animals, beginning about the 10th day. Epilation was seen in about 25 percent of the animals. Marked ulcerative lesions on the labial and buccal mucosa and on the dorsum of the tongue were found in some animals.

Table V. Mortality Distributions

Radiation field	Total mortality	Intervals of deaths (days)		
		0-9	10-19	20-30*
x-ray	35	1	31	3
reactor	37	0	36	1

* No deaths after 30 days

Each decedent in this study was necropsied. Hemorrhage and evidences of infection were the most prominent gross changes seen. Petechial hemorrhages were almost invariably found in the integument, gastrointestinal tract, and selected major organs. Diffuse subendocardial and myocardial hemorrhages were seen in the left heart of most of the animals. A representative listing of lesions associated with infection is as follows:

- Ulceration of the oral cavity and of the cecal and colonic mucosa.
- Pulmonary adhesions and pneumonias.
- Occasional pustular abscesses in the major organs.

CONCLUSIONS

Under the conditions of this study, it was concluded that for the Macaca mulatta:

- The median lethal dose is 503 rads for x rays and 381 rads for reactor radiations.
- The acute mortality RBE of reactor radiations as determined by the ratio of midlethal doses measured at the midline of a homogeneous Plexiglas phantom was 1.3.
- Acute radiation death from lethal range x-ray or reactor radiations exposures will almost invariably occur between the 10th and 20th postirradiation day.
- Deaths from lethal range exposures will rarely occur in the 30 to 60-day postirradiation interval.
- Vomiting usually occurs within 3 hours after irradiation of the nonfasted monkey.
- Radiation quality differences were not discernible in the mode of death, survival time, clinical symptoms, or gross pathology.

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13. ABSTRACT

One hundred and forty young adult male and female monkeys (Macaca mulatta) were irradiated with single whole-body doses of mixed gamma-neutron radiations or 250 kVp x rays. The 80 mixed gamma-neutron and 60 x irradiated animals were uniformly exposed in groups of 10 to graded doses delivered at the rate of 16 and 20 rads per minute respectively while being slowly rotated in an upright position. Referenced to the midline of a Plexiglas monkey phantom, $LD_{50/60}$ values of 503 ± 20 rads and 381 ± 13.5 rads were calculated for x-ray and mixed gamma-neutron radiations, respectively. Using 250 kVp x ray as the reference source, the acute mortality Relative Biological Effectiveness of mixed gamma-neutron radiations as determined by the ratio of midline rad doses in a Plexiglas phantom was 1.3.

Ninety-three percent of the deaths occurred in the 10 - 19-day interval resulting in a mean survival time of approximately 15 days with no deaths occurring after 28 days.

From the comparative data on clinical observations, survival time, gross pathology of the decedents and serial hemograms of the survivors during the 30 - 60-day intervals, no significant difference in response was apparent in the x- or mixed gamma-neutron irradiated monkey. Further, death, with one exception, was concluded to be principally attributable to hematopoietic injury with infection as the major contributing lethal factor.

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